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BINGEN (DE). SOARE, Lucica, Cristina [RO/CH]; Rue  
Davel 21, CH-1004 LAUSANNE (CH).

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(74) Common Representative: BOEHRINGER INGEL-  
HEIM PHARMA GMBH & CO.KG; Binger Str. 173,  
55216 INGELHEIM (DE).

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(71) Applicants (*for all designated States except US*):  
BOEHRINGER INGELHEIM PHARMA GMBH &  
CO.KG [DE/DE]; Binger Str. 173, 55216 INGELHEIM  
(DE). ÉCOLE POLYTECHNIQUE FÉDÉRALE DE  
LAUSANNE (EPFL) [CH/CH]; SRI, CM-Ecublens,  
CH-1015 LAUSANNE (CH).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): JONGEN, Nathalie  
[BE/CH]; Route de Genève 64 B, CH-1028 PRÉV-  
ERENGES (CH). LEMAÎTRE, Jacques [BE/CH];  
Chemin de la Fauvette 30 F, CH-1012 LAUSANNE (CH).  
BOWEN, Paul [CH/CH]; Route du Boiron 23, CH-1260  
NYON (CH). DONNET, Marcel [CH/CH]; Route de  
Genève 5, CH-1033 CHESEAUX (CH). SCHIEWE,  
Jörg [DE/DE]; Rieslingstrasse 60, 55129 MAINZ (DE).  
ZIERENBERG, Bernd [DE/DE]; Goethestr. 1, 55411

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(54) Title: PROCESS FOR THE MANUFACTURE OF POWDERS OF INHALABLE MEDICAMENTS

(57) Abstract: The invention relates to an improved process for the production of powders of an inhalable medicament by crystalliza-  
tion from a supersaturated fluid containing said medicament; the method comprising passing along a tubular reactor (a) a segmented  
flow of that fluid comprised of discrete volumes; or (b) a fluid mixture being separated by discrete volumes of a separating fluid  
which is substantially immiscible with said fluid; characterized in that the crystallization is initiated by application of ultrasound.

## Process for the Manufacture of Powders of Inhalable Medicaments

### BACKGROUND OF THE INVENTION

#### 1. TECHNICAL FIELD

The invention relates to an improved process for the production of powders organic compounds by precipitation from liquid mixtures.

#### 2. BACKGROUND INFORMATION

The international patent application WO 98/2237 discloses a process for the production of inorganic powders by precipitation from a liquid reaction mixture, the method comprising passing along a tubular reactor a segmented reaction flow comprised of discrete volumes of the reaction mixture separated by discrete volumes of a separating fluid which is substantially immiscible with said reaction mixture, the residence time of said discrete volumes of reaction mixture in the reactor being sufficient for the precipitation reaction to be effected.

Unfortunately, this process is not applicable for inhalable medicaments.

For inhalable medicaments a well-defined size and shape of the crystals is a pre-requisite. Inhalatives require a certain form of the medicament. For example, micronised medicaments or active ingredients generally come in solid form. In order to guarantee the inhalability of the medicament, high requirements are placed on the particle size, the particle size distribution, the morphology, the stability and the flow performance.

In general, the entire administered dose of the medicament does not reach the lungs, rather only a part of this does. The particle size has a substantial influence on the proportion of the medicament which actually reaches the lungs. For this reason, particles are preferred which have a diameter of less than 20  $\mu\text{m}$ , preferably less than 5  $\mu\text{m}$  and greater than 0.3  $\mu\text{m}$ . The diameter of the particle should be within the given window and furthermore

should have the narrowest possible size distribution. Larger particles are separated off during respiration in the upper airways whilst smaller particles are not deposited in the lungs and these leave again when exhaling.

- 5 Therefore, there is a great requirement for processes which achieve powders of inhalable medicaments with uniform shape, small size and narrow size distribution.

It is known that crystallization of drug actives can be ultrasonically promoted, e.g. Causland and Cains in Drug Delivery systems & sciences, volume 2 no 2, June/ July 2002,  
10 pp 47-51.

However, there is no hint that the application of ultrasound to a tubular reactor with a segmented reaction flow would yield such a desired crystal formation.

## 15 BRIEF SUMMARY OF THE INVENTION

It has now be found surprisingly, that the application of ultrasound to a tubular reactor with a segmented reaction flow achieves crystals of inhalable medicaments with the desired shape and size.

- 20 Therefore, the invention relates to an improved process for the production of powders of inhalable medicaments by crystallization from a supersaturated fluid containing said medicament, the method comprising passing along a tubular reactor

- (a) a segmented flow of that fluid comprised of discrete volumes; or
- (b) a fluid mixture being separated by discrete volumes of a separating fluid

- 25 which is substantially immiscible with said fluid,  
characterized in that the crystallization is initiated by application of ultrasound.

A second embodiment of the present invention is a micro-reactor for implementing the process according to this invention comprising a micro-mixer, a segmenter and a tubular reactor, wherein

- the dimensions of the micro-mixer for dividing the added fluids which are to be mixed is in the range of 10  $\mu\text{m}$  to 1 mm, preferably between 25  $\mu\text{m}$  to 200  $\mu\text{m}$ ,
- the dimensions of the channels of the segmenter lie in the range of 0.1 to 5 mm, preferably in the range of between 0.2 mm and 5 mm, and

the tubular reactor is configured to be tube-, pipe- or channel-shaped with diameters of the channels in the range of 0.5 to 10 mm, preferably 1 mm to 2 mm, and with a length of between 10 cm and 200 m, preferably between 1 m and 25 m and is equipped with an external ultrasound source.

Furthermore the invention relates to an inhalable medicament with an aerodynamic diameter of less than 20  $\mu\text{m}$ , preferably less than 5  $\mu\text{m}$  and greater than 0.3  $\mu\text{m}$ , characterized in that it is produced by means of the inventive process.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic flow chart of fenoterol crystallization.

Figure 2 shows the X-Ray diffractogram of dried sample of fenoterol (SFTR-13.06.02) Tween (Polysorbate) and the reference powder.

Figure 3 shows the SEM image of dried material of fenoterol (SFTR-13.06.02) Tween

Figure 4 shows a schematic flow chart of Budesonide (11.07.02-SFTR) crystallization

Figure 5 shows the X-rays diffractogram of budesonide powder crystallised and reference material.

#### DETAILED DESCRIPTION OF THE INVENTION

The invention preferably relates to a process wherein the segmented flow passes along the tubular reactor as a plug flow.

Furthermore preferred is a process wherein the tubular reactor consists of the following segments:

- (i) a residence time ( $t_R$ ) segment;

- (ii) an ultrasound time ( $t_{US}$ ) segment, in particular wherein  $t_{US}$  is 1 to 30 s or wherein  $t_{US}$  is 0.5 to 15 min and  $t_A$  is 0 to 30 s; and
- (iii) optionally an aging time ( $t_A$ ) segment.

5 The particle size distribution of the organic compounds can be fine-tuned depending on the ratio of  $t_R$ ,  $t_{US}$  and  $t_A$ . Smaller particle size distributions can be obtained if longer  $t_{US}$  are applied.

Preferably an ultrasound with a frequency of 20 to 60 kHz and/or an energy density from  
10 10 to 80  $WL^{-1}$  is applied.

Another preferred embodiment is a process wherein the segmented flow or a precursor segmented flow from which the segmented flow is subsequently generated, is produced by passing the fluid containing the organic compound or a component thereof and the  
15 separating fluid to a chamber having a restricted outlet from which the segmented flow issues, in particular wherein the segmented flow is produced in a segmentation arrangement comprised of two concentric tubes, said chamber being provided at the outlet of the inner of the tubes and said chamber has an internal diameter of 2 mm to 10 mm.

20 Preferably, the innermost tube has an internal diameter of 0.1 to 2 mm and/or the distance between the outlet of the innermost tube and the inlet of the restriction is in the range 0.1 to 5 mm.

Preferably the separating fluid is passed to said chamber along the innermost tube.  
25

Furthermore preferred is a process wherein the segmented flow is prepared by passing the fluid containing the organic compound and the separating fluid to said chamber thereby producing the segmented reaction flow, in particular wherein discrete volumes of said

component of the fluid comprising the organic compound are separated by discrete

30 volumes of the separating fluid and the segmented reaction flow is produced by admixing

said discrete volumes of the fluid containing said organic compound with the remaining component(s) of the mixture.

Another preferred embodiment is a process wherein the segmented reaction flow is prepared from said precursor flow by injecting said latter flow and the further component(s) of the fluid containing the medicament to a chamber having a restricted outlet under conditions such that said further component(s) of the reaction mixture become admixed with the discrete volumes of said first component of the reaction mixture whereby the segmented reaction flow is produced, in particular wherein the segmented reaction flow is produced in a mixing arrangement, in particular wherein the chamber of the mixing arrangement has a diameter of 9 mm to 10 mm, having preferably an internal diameter of 0.1 to 2 mm, comprised of two concentric tubes said chamber being provided at the outlet of the inner of the two tubes; and/or wherein the distance between the outlet of the innermost tube of the mixing arrangement and the inlet of the restriction is in the range 0.1 to 5 mm.

Furthermore preferred is a process wherein a fluid mixture containing the medicament is prepared in a micro-mixer before the segmentation, in particular wherein the fluid mixture is a mixture of a solution of the medicament with a suitable precipitant to create a metastable supersaturated fluid.

Another preferred embodiment is a process wherein the fluid mixture is a mixture of a solution of the medicament with a suitable detergent in order to influence particle size and shape during the subsequent crystallization process.

25

Preferably the separating fluid is

a hydrocarbon, in the event that the organic compound is water-soluble, in particular a C<sub>6-18</sub> hydrocarbon; or

a lower alcohol or water, in the event that the organic compound is insoluble in water.

30

In the following text, examples are listed for the active ingredients, the adjuvants, the solvent and the precipitation agent.

The following are used as medicaments or active ingredients:

5

- as anticholinergics: ipratropiumbromide, oxitropium, tiotropiumbromide, tiotropiumbromide-monohydrate,

10

- as betasympathomimetics: bambuterol, biolterol, carbuterol, formoterol, clenbuterol, fenoterol, hexoprenalin, procaterol, ibuterol, pirbuterol, tulobuterol, reproterol, salbutamol, salmeterol, sulfonterol, terbutalin, orciprenalin, 1-(2-fluoro-4-hydroxy-phenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethyl-phenyl)-2-tert.-butyl-amino)ethanol, 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol,

15

- as antiallergics: disodiumchromeglicate, nedocromil, epinastin, and

20

- as steroids: flunisolide, dexamethasone-21-isonicotinate, seratrodist, mycophenolate mofetil, pranlukast, zileuton, butixocort, budesonide, deflazacort, fluticasone, proedrol, mometasin furoate, tipredan, beclomethasone (or the 16,21-dipropionate), beclomethasone, Douglas, icomethasone enbutate, cyclometasone, cloprednol, fluocortin butyl, halometasone, deflazacort, alclometasone, cyclometasone, alisactide, prednicarbate, hydrocortisone-butyratepropionate, tixocortolpivalate, alclometasone-dipropionate, lotrisone, canesten-HC, deprodone, fluticasone-propionate, methylprednisolone-aceponate, halopredone-acetate, mometasone, mometasone-furoate, hydrocortisone-aceponate,

25

30

mometasone, ulobetasol-propionate, aminogluethimide, triamcinolone, hydrocortisone, meprednisone, fluorometholone, dexamethasone, betamethasone, medrysone, fluclorolone acetonide, fluocinolone acetonide, paramethasone-acetate,

deprodon propionate, aristocort-diacetate, fluocinonide, mazipredone,  
 difluprednate, betamethasone valerate, dexamethasoneisonicotinate,  
 beclomethasone-dipropionate, fluocortoloncapronate, formocortal, triamcinolon-  
 hexacetonide, cloprednol, formebolone, clobetasone, endrisone, flunisolide,  
 5 halcinonide, fluazacort, clobetasol, hydrocortisone-17-butyrate, diflorasone,  
 fluocortin, amcinonide, netamethasone dipropionate, cortivazole,  
 betamethasoneadamantoate, fluodexane, trilostan, budesonide, clobetasone,  
 demetex, trimacinolone benetonide, 9.alpha.-chloro-6.alpha.-fluoro-  
 11.beta.17.alpha.-dihydroxy-16.-alpha.-methyl-3-oxo-1,4-androstadiene-17.beta.-  
 10 carboxy acid methylester-17-propionate, ST-126.

Other medicaments produced with the process according to the invention are montelukast  
 and pramipexol.

15 As adjuvants for inhalatives, especially lactose, glucose, sucrose, mannitol and/or trehalose  
 are used.

Examples of solvent and precipitation agents, depending on the medicaments which are to  
 be produced, are shown in the following tables, wherein solvents and precipitation agents  
 20 must be miscible.

For anticholinergics/betasymphathomimetics/ antiallergics:

Active Ingredient	Solvent	Precipitating Agents
Salt forms	Water, methanol	Alcohols (ethanol, propanol, iso-propanol), ketones (acetone, butanone)
Free bases	Alcohols (ethanol, propanol, iso-propanol,	Water, methanol



	tert.-butanol), ketones (acetone, butanone)	
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For steroids:

Active Ingredient	Solvent	Precipitating Agents
Polars	Ketones (acetone, butanone)	Alcohols (methanol, ethanol)
	Alcohols (ethanol, propanol, iso-propanol, tert.-butanol), ketones (acetone, butanone)	Water, methanol
	Aromatics (toluene, ethylbenzene)	Alcohols (ethanol, propanol, iso-propanol)
Unpolar	Halogen hydrocarbons (dichloromethane, trichloromethane)	Alcohols (ethanol, propanol, iso-propanol), ether (dimethylether, dioxane)

5

Examples of transport media are shown in the following tables, dependent on the active ingredients which are to be produced and the solvents which are used, wherein solvents and transport media are not miscible.

Active Ingredients	Solvents	Transport Media
Polar	Water, alcohols (methanol, ethanol iso-propanol, tert.-butanol), ketones (acetone,, propanol, butanone)	Fluids: hydrocarbons (benzene, petrolether, cyclohexane, decaline, dodecane, benzene, toluene, xylene)

		Gases: air, nitrogen, carbon dioxide, helium, argon
Unpolar	Halogen hydrocarbons (dichloromethane, trichloromethane), ether (diethylether, dibutylether), aromatics (toluene, ethylbenzene)	Fluids water, alcohols (methanol), amides (formamide) Gases: air, nitrogen, carbon dioxide, helium, argon

Procedures by way of examples and drawings carrying out the process according to the invention will be described in more detail hereinafter. The Examples which follow serve solely as a detailed illustration without restricting the subject matter of the invention.

### Example 1

#### Continuous crystallization of inhalable fenoterol HBr using a microreactor

In order to crystallize fenoterol HBr with a particle size suitable for inhalation (90 % of all crystals are smaller than  $5.8 \mu\text{m}$ ) a segmented flow tubular reactor was used. Fenoterol was crystallized from water by cooling, dodecane has been used as transport medium for segmentation and formation of small water bubbles.

The following parameters must be employed in order to achieve a crystal size small enough to be suitable for inhalation:

- the starting material must be a solution with a high concentration of fenoterol in water (695 mg/ml, prepared at  $90^\circ\text{C}$ ), which in fact represents a liquid two phase mixture
- an additive (dodecane, 6 % v./v.) needs to be added to the hot solution
- from this solution a very high supersaturation is created by rapid cooling down to  $18^\circ\text{C}$
- the cooled homogeneous supersaturated solution is then allowed to rest for 22 minutes
- crystallization is induced inside small bubbles of solution by ultrasonication, the ultrasound is applied for 14 minutes

- the suspension formed is stabilized by addition of water containing a detergent (0.1 w.-% tween)

## 5 Experimental:

The experiments were performed by dissolving 34.5 g fenoterol HBr in 50 ml of water. The solution was heated up to 90 °C in a thermostatic bath under nitrogen gas flow to dissolve the fenoterol. 3 ml of dodecane are added to the solution before the start of the experiment.

- 10 The solution is pumped through the reactor and enters the segmenter where small droplets are formed by segmentation with a transport fluid, dodecane at 18 °C. The droplets travel for 22 minutes through the tube before being treated for 14 minutes with ultrasound. Upon ultrasound treatment a highly concentrated suspension is formed inside the water phase which leaves the reactor together with the transport medium. The separation between
- 15 the slurry and the transport medium was made in an open beaker to which pure water or an aqueous solution of 0.1 w.-% of tween 80 (polyethylenglycole (20) S monooleate) was added (with a (dodecane + slurry)/water ratio of about one) (see Figure 1).

## Results:

- 20 Table 1 presents the particle size distribution measured in aqueous suspension.

**Table 1: Particle size distribution data determined in suspension measured with the Malvern Mastersizer**

Sample	d <sub>v10</sub> (μm)	d <sub>v50</sub> (μm)	d <sub>v90</sub> (μm)	Span	Medium
SFTR-14.05.02	1.21	2.51	5.20	1.59	aqueous suspension
SFTR-13.06.02	0.77	1.70	5.92	3.03	tween stabilized aqueous suspension

- 25 The sample was also characterized by X-ray diffraction and thermoanalysis. The powder produced by filtration and drying of the suspension was fully crystalline and conform to the starting material (figure 2)

Furthermore, DSC and TGA show equivalence between starting material and crystallization product. Figure 3 shows a SEM image of the powder.

## 5 Example 2

### **Continuous crystallization of inhalable budesonide using a microreactor**

Budesonide was crystallized from ethanol by a combined antisolvent and cooling crystallization using the segmented flow tubular reactor.

The following parameters must be employed in order to achieve a small crystal size:

- 10 - the starting material must be a solution with a high concentration of budesonide in ethanol (60 mg/ml, prepared at 60°C)
- an additive (hydroxy-propyl cellulose, 1 w.-% ) needs to be added to the hot solution
- from this solution a very high supersaturation is created by mixing with water (1:1) as antisolvent and simultaneous cooling down to 11°C
- 15 - the cooled homogeneous supersaturated solution is then allowed to rest only for 30 seconds
- crystallization is induced inside small bubbles of solution by ultrasonication, the ultrasound is applied for 12 minutes

20

#### Experimental:

3 g budesonide were dissolved in 50 ml of ethanol at 60°C and allowed to cool to 40 °C. 50 ml water containing 1 w.-% of hydroxy-propyl cellulose were used as antisolvent and cooled down to 10 °C.

- 25 The dodecane was saturated with ethanol prior to the experiment to avoid a diffusion of the ethanol into the dodecane phase. The dodecane was injected at the temperature of 11 °C and the thermostatic bath around the tubular section of the segmented flow tubular reactor was also maintained at 11 °C. The warm ethanolic solution of budesonide was mixed with cold antisolvent using a 2-jet mixer at a volume ratio ethanol/water of 1:1. The droplets  
30 were allowed to travel through the tube for 30 seconds before they undergo an ultrasonic treatment of 12 minutes where the tube is placed in an ultrasonic bath (cp. Figure 4). The

budesonide suspension together with the transport medium were collected in a beaker maintained at 10 °C. This suspension was filtered and dried over silica gel at room temperature. The powder yield is 60%.

5

#### Results:

The particle size distribution in the suspension produced has not been measured. Table 2 shows the particle size distribution of the dry powder re-dispersed in water containing  
10 0.1 w.-% tween. The size distribution may be different compared to the crystals in suspension due to agglomeration during drying.

*Table 2: Particles size distribution data of budesonide powder.*

Sample	d <sub>v10</sub> (µm)	d <sub>v50</sub> (µm)	d <sub>v90</sub> (µm)	Span
Budesonide	1.32	7.59	12.86	1.52

15 The sample was also characterized by X-ray diffraction. The powder produced by filtration and drying of the suspension was fully crystalline and conform to the starting material (figure 5).

## CLAIMS:

1. An improved process for the production of powders of inhalable medicaments by crystallization from a supersaturated fluid containing said medicament, the method comprising passing along a tubular reactor
- 5 (a) a segmented flow of that fluid comprised of discrete volumes; or  
(b) a fluid mixture being separated by discrete volumes of a separating fluid which is substantially immiscible with said fluid, characterized in that the crystallization is initiated by application of ultrasound.
- 10 2. A process as claimed in claim 1 wherein the segmented flow passes along the tubular reactor as a plug flow.
3. A process as claimed in claim 1 or 2 wherein the tubular reactor consists of
- 15 the following segments:  
(i) a residence time ( $t_R$ ) segment;  
(ii) an ultrasound time ( $t_{US}$ ) segment; and  
(iii) optionally an aging time ( $t_A$ ) segment.
- 20 4. A process as claimed in any one of claims 1 to 3 wherein  $t_{US}$  is 1 to 30 s and  $t_A$  is 0.5 to 15 min.
5. A process as claimed in any one of claims 1 to 3 wherein  $t_{US}$  is 0.5 to 15 min and  $t_A$  is 0 to 30 s.
- 25 6. A process as claimed in any one of claims 1 to 5 wherein ultrasound with a frequency of 20 to 60 kHz is applied.
7. A process as claimed in any one of claims 1 to 6 wherein the energy density
- 30 of the ultrasound applied is from 10 to 80  $WL^{-1}$ .

8. A process as claimed in any one of claims 1 to 7 wherein the segmented flow or a precursor segmented flow from which the segmented flow is subsequently generated, is produced by passing the fluid containing the organic compound or a component thereof and the separating fluid to a chamber having a restricted outlet from which the segmented flow issues.

9. A process as claimed in any one of claims 1 to 8 wherein a fluid mixture containing the organic compound is prepared in a micro-mixer before the segmentation.

10. A process as claimed in any one of claims 1 to 9 wherein the fluid mixture is a mixture of a solution of the organic compound with a suitable precipitant to create a meta-stable supersaturated fluid.

11. A process as claimed in any one of claims 1 to 10 wherein the fluid mixture is a mixture of a solution of the organic compound with a suitable detergent in order to influence particle size and shape during the subsequent crystallization process.

12. A process as claimed in any one of claims 1 to 11 wherein the separating fluid is a hydrocarbon, in the event that the organic compound is water-soluble; or a lower alcohol or water, in the event that the organic compound is insoluble in water.

13. A process as claimed in claim 12 wherein the separating fluid is a C<sub>6-18</sub> hydrocarbon.

14. A process as claimed in any one of claims 1 to 15 wherein the organic powder is an inhalable medicament selected from the group consisting of anticholinergics, betasympathomimetics, antiallergics and steroids.

15. A micro-reactor for implementing the process according to one of the preceding claims comprising a micro-mixer, a segmenter and a tubular reactor, wherein

- the dimensions of the micro-mixer for dividing the added fluids which are to be mixed is in the range of 10  $\mu\text{m}$  to 1 mm, preferably between 25  $\mu\text{m}$  to 200  $\mu\text{m}$ ,
- the dimensions of the channels of the segmenter lie in the range of 0.1 to 5 mm, preferably in the range of between 0.2 mm and 5 mm, and
- the tubular reactor is configured to be tube-, pipe- or channel-shaped with diameters of the channels in the range of 0.5 to 10 mm, preferably 1 mm to 2 mm, and with a length of between 10 cm and 200 m, preferably between 1 m and 25 m and is equipped with an external ultrasound source.

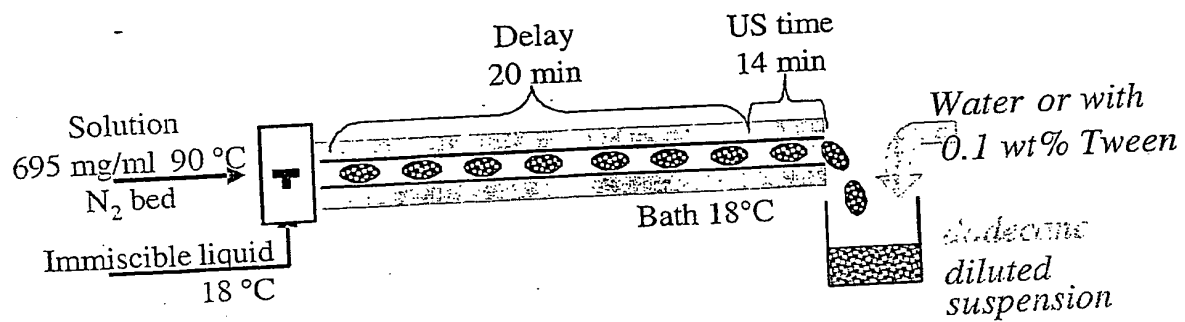
16. A micro-reactor according to claim 15, wherein the tubular reactor consists of the following segments:

- (i) a residence time ( $t_R$ ) segment;
- (ii) an ultrasound time ( $t_{US}$ ) segment; and
- (iii) optionally an aging time ( $t_A$ ) segment.

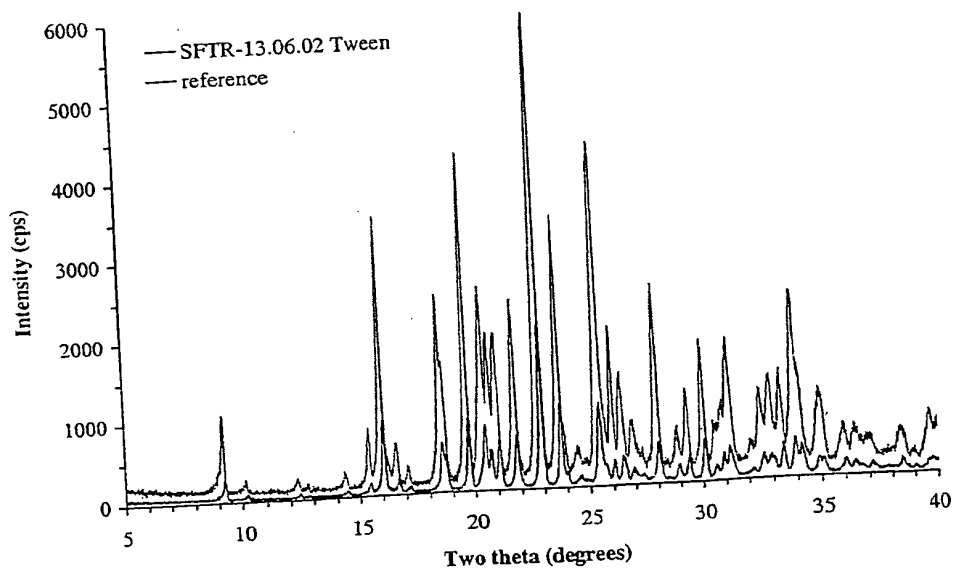
17. A micro-reactor according to claim 16, wherein the ultrasound time ( $t_{US}$ ) segment is inserted into an ultrasound bath.

18. Inhalable medicament with an aerodynamic diameter of less than 20  $\mu\text{m}$ , preferably less than 5  $\mu\text{m}$  and greater than 0.3  $\mu\text{m}$ , characterized in that it is produced by means of a process according to one of claims 1 to 14.





5 Fig. 1



10 Fig. 2

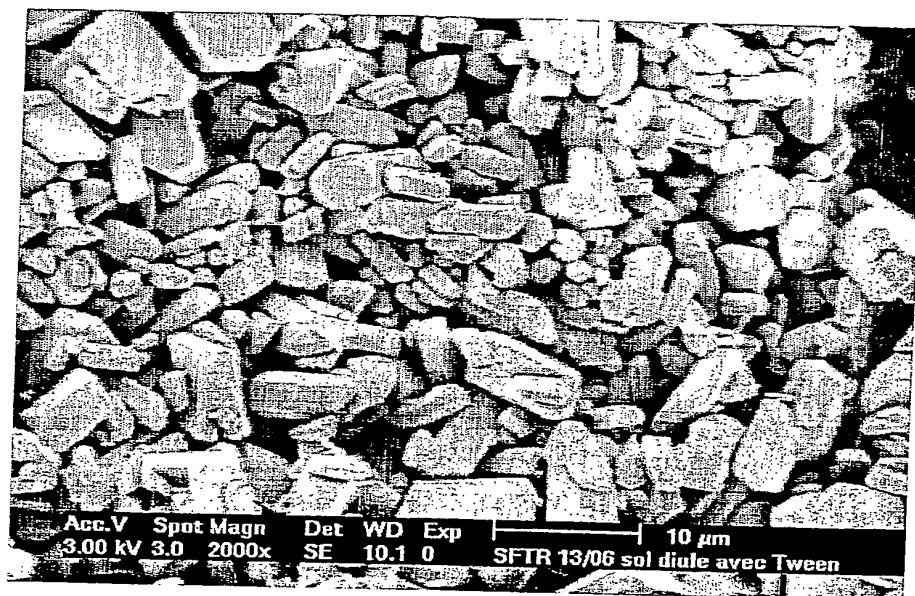
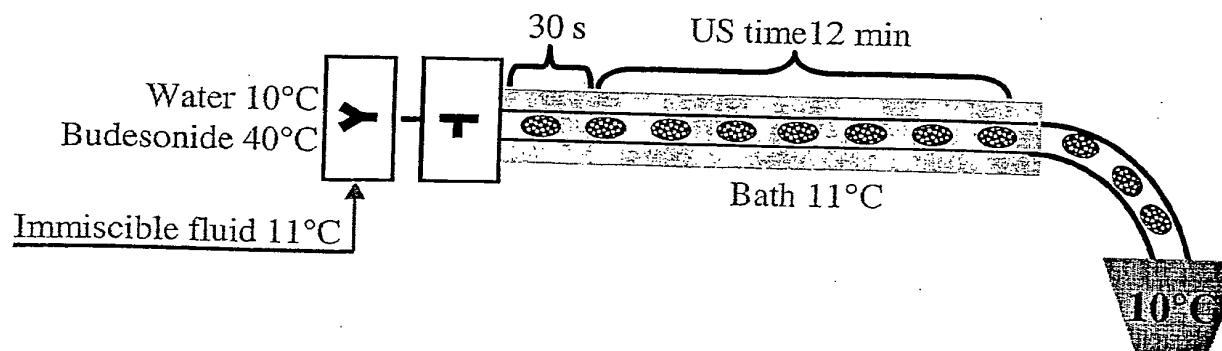


Fig. 3



5 Fig. 4

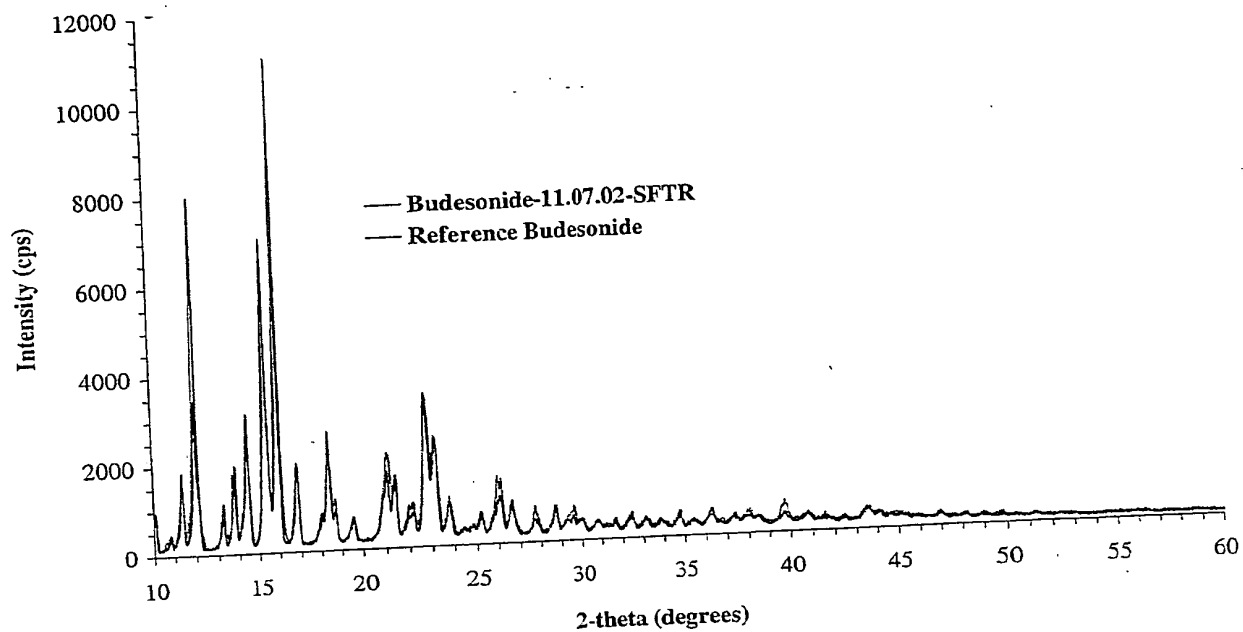


Fig. 5

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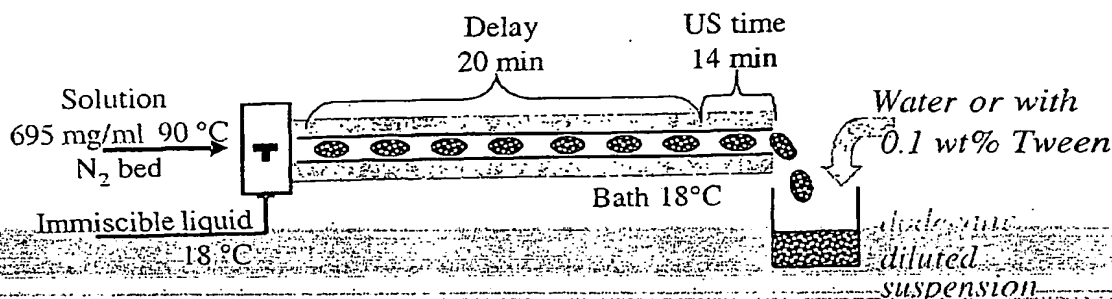
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- (71) Applicants (for all designated States except US): **BOEHRINGER INGELHEIM PHARMA GMBH & CO.KG** [DE/DE]; Binger Str. 173, 55216 INGELHEIM (DE). **ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE (EPFL)** [CH/CH]; SRI, CM-Ecublens, CH-1015 LAUSANNE (CH).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **JONGEN, Nathalie** [BE/CH]; Route de Genève 64 B, CH-1028 PRÉVERENGES (CH). **LEMAÎTRE, Jacques** [BE/CH]; Chemin de la Fauvette 30 F, CH-1012 LAUSANNE (CH). **BOWEN, Paul** [CH/CH]; Route du Boiron 23, CH-1260 NYON (CH). **DONNET, Marcel** [CH/CH]; Route de Genève 5, CH-1033 CHESEAUX (CH). **SCHIEWE, Jörg** [DE/DE]; Rieslingstrasse 60, 55129 MAINZ (DE). **ZIERENBERG, Bernd** [DE/DE]; Goethestr. 1, 55411 BINGEN (DE). **SOARE, Lucica, Cristina** [RO/CH]; Rue Davel 21, CH-1004 LAUSANNE (CH).
- (74) Common Representative: **BOEHRINGER INGELHEIM PHARMA GMBH & CO.KG**; Binger Str. 173, 55216 INGELHEIM (DE).
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(54) Title: PROCESS AND REACTOR FOR THE MANUFACTURE OF POWDERS OF INHALABLE MEDICAMENTS



(57) Abstract: The invention relates to an improved process for the production of powders of an inhalable medicament by crystallization from a supersaturated fluid containing said medicament, the method comprising passing along a tubular reactor (a) a segmented flow of that fluid comprised of discrete volumes; or (b) a fluid mixture being separated by discrete volumes of a separating fluid which is substantially immiscible with said fluid, characterized in that the crystallization is initiated by application of ultrasound.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/11010

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 B01D9/00 B01J2/06 B01J19/00 B01J19/10 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B01J B01D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

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Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel: (+31-70) 340-2040; Tx: 31.65 F-epo nl  
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**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

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